Gene Discovery for Complex Neurological and Neurobehavioral Disorders

The goal of this program announcement (PA) is to promote the identification of susceptibility genes for complex neurological and neurobehavioral disorders. For this PA, complex disorders are defined as those caused by the interaction of multiple genes or by a combination of genetic and environmental risk factors. Many of these disorders are relatively common and clinically heterogeneous. Projects focusing on any phase of the gene discovery process, from initial patient ascertainment to positional cloning, are appropriate. Novel approaches, including the use of intermediate phenotypes that potentially underlie complex disorders, are also encouraged.

Genetic factors contribute to a broad spectrum of neurological and neurobehavioral diseases. During the last decade, genes that cause many single-gene neurological disorders have been identified (e.g., Huntington disease, neurofibromatosis, Rett syndrome). For these disorders, familial inheritance patterns follow the rules of Mendelian segregation. For many common disorders (e.g., stroke, Parkinson disease, epilepsy, Alzheimer disease, attention deficit/hyperactivity disorder), inheritance patterns are more complex, and progress in identifying genes that affect susceptibility and disease outcome has been slow. Such disorders appear to be caused by multiple genes or by a combination of genetic and environmental factors.

The wealth of genomic information becoming available through the Human Genome Project is providing a powerful tool for gene discovery. Once disease susceptibility genes are identified, it will be possible to study gene function, investigate disease pathophysiology, and explore strategies for therapeutic intervention. Gene identification will also provide a basis for improved diagnostic classification, genetic counseling, and understanding of pharmacogenetic interactions.

Applications submitted in response to this PA should focus on the identification of susceptibility genes that contribute to genetically complex disorders affecting the nervous system or to the phenotypes that underlie these disorders. Proposed studies can involve the initial collection of biomaterials and clinical information from a patient population or the subsequent application of genetic or molecular strategies for gene localization. Possible methodologies include, but are not limited to, traditional linkage analysis, sibling pair and affected-pedigree-member methods, case–control or family-based association studies, linkage disequilibrium mapping in genetically isolated populations, candidate gene analysis, cytogenetic studies to identify chromosomal abnormalities associated with a disorder, and positional cloning. This PA focuses on human studies; projects using invertebrate or vertebrate animal models are not appropriate. As gene discovery requires collaborations among epidemiologists, geneticists, clinicians, molecular biologists, and other researchers, multidisciplinary projects are encouraged.

Because complex disorders are clinically and genetically heterogeneous, the identification of susceptibility genes by standard genetic methodologies has been difficult. Therefore, the development of novel approaches and the use of state-of-the-art technologies are essential. An example of such an emerging strategy is the use of intermediate phenotypes (endophenotypes) to facilitate gene discovery. Endophenotypes are characteristics that may represent more proximal readouts of gene function. Examples include enzyme activities, plasma levels of particular neurotransmitters, changes in gene expression, structural or functional phenotypes detected by brain imaging, and behavioral or cognitive deficits. Classifying patients based on such parameters has, in certain cases, accelerated the process of gene discovery. The use of this strategy is appropriate if the applicant 1) demonstrates that the phenotype in question can be reliably and accurately measured, 2) provides evidence suggesting that the phenotype underlies a particular neurological or neurobehavioral disorder or group of disorders, and 3) makes a strong case that use of this phenotype will facilitate the discovery of susceptibility genes.

Applications should focus on complex neurological or neurobehavioral disorders relevant to the research missions of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), the National Institute on Drug Abuse (NIDA), or the NIEHS. A partial list of diseases of interest to the NINDS for this PA is given in Appendix A of the planning document "Neuroscience at the New Millennium" (http://www.ninds.nih.gov/about_ninds/strategic_plan.htm). These include neurological disorders (e.g., stroke, Parkinson disease, epilepsy, multiple sclerosis, Alzheimer disease) and neurobehavioral disorders (e.g., autism, attention deficit/hyperactivity disorder, Tourette syndrome). Disorders of interest to the NIA for this PA include Alzheimer disease and other age-associated neurodegenerative, cognitive, and motor system disorders (see http://www.nia.nih.gov/research/extramural/neuroscience/programs.htm and http://www.nia.nih.gov/strat-plan/2001-2005/). Disorders of interest to the NIDA for this PA include drug abuse and/or drug dependence on stimulants (e.g., cocaine, amphetamine), narcotics (e.g., opiates), nicotine, benzodiazepines, barbiturates, cannabis, hallucinogens, and/or multiple drugs of abuse in human beings. Intermediate phenotypes of interest to the NIDA include, but are not limited to, sensation seeking, impulse control, responses to rewarding stimuli as measured by neuroimaging, and initial reactivity to drug exposure. Disorders of interest to the NIEHS for this PA are Parkinson disease, amyotrophic lateral sclerosis, attention deficit/hyperactivity disorder, autism and autism spectrum disorders, and other neurodegenerative disorders when the focus of the gene discovery is on those genes that can be influenced by environmental exposures contributing to the onset of the disorder(s).

An important resource available to applicants is the Center for Inherited Disease Research (CIDR), a centralized facility established to provide high-throughput genotyping and statistical genetics services. The CIDR was established in 1996 as a joint effort of eight NIH institutes and is supported through a contract to The Johns Hopkins University. The CIDR is available to all investigators through competitive peer review by a chartered CIDR Access Committee. Projects are evaluated based on the need for high-throughput genotyping and the likelihood that genotyping will lead to successful mapping of genes contributing to that disease. Because the NINDS, the NIA, and the NIDA support the CIDR, research projects funded by these institutes under this PA are eligible for no-cost genotyping. Further information about the CIDR may be found at http://www.cidr.jhmi.edu/. Submission deadlines for applications requesting CIDR access are November 1, March 1, and July 1. An approval letter from the CIDR Access Committee may then be included in the application.

Sharing of biomaterials, data, and software in a timely manner has been an essential element in the rapid progress that has been made in the genetic analysis of human diseases. PHS policy requires that investigators make unique research resources available for research purposes to qualified individuals within the scientific community when they have been published (see the NIH Grants Policy Statement at http://grants.nih.gov/grants/guide/notice-files/not96-184.html). In addition, the NIH recently released a statement on the sharing of research data that applies to all investigator-initiated applications with direct costs greater than $500,000 in any single year (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html).

All applicants who respond to this PA must propose plans for sharing data and biomaterials generated through the grant. Applicants should explain how funds for the storage and distribution of data and biomaterials will be obtained, and may request such funds in the budget of the application. It is expected that the information to be shared will include clinical, diagnostic, and pedigree structure information. Biomaterials to be shared should include patient DNAs and cell lines. When possible, data and biomaterials should be placed in databases or repositories that will permit their efficient distribution to investigators throughout the scientific community. An example of such a facility is the NINDS Human Genetics Resource Center (http://locus.umdnj.edu/ninds). Rapid sharing of data and biomaterials is strongly encouraged.

Phenotyping subjects for the analysis of complex diseases presents numerous challenges. It is expected that applicants will use the most sophisticated methodologies currently available for a particular disorder. When possible, applicants are encouraged to include the following methodological features in their proposals: 1) use of a structured or semistructured diagnostic interview with patients or other informants (it is expected that such procedures will greatly facilitate the establishment of a reliable diagnosis, and thus will increase the statistical power and utility of the data set for genetic analysis); 2) comprehensive synthesis of information systematically collected from laboratory procedures, structured or semistructured clinical interviews of high reliability, medical records, and multiple informants; and 3) entry of comprehensive phenotypic data described above into a computerized database that may be easily shared with other researchers.

This PA will use the NIH research project grant (R01) and exploratory/developmental grant (R21) award mechanisms. The R21 mechanism is intended to encourage new exploratory/developmental research projects by providing support for the early stages of their development. For example, such projects could assess the feasibility of a novel area of investigation or a new experimental system that has the potential to enhance health-related research. These studies may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of biomedical, behavioral, or clinical research.

Applications for R21 awards should describe projects distinct from those supported through the traditional R01 mechanism. For example, long-term projects or projects designed to increase knowledge in a well-established area will not be considered for R21 awards. Applications submitted

under this mechanism should be exploratory and novel. These studies should break new ground or extend previous discoveries toward new directions or applications.

R21 applications may request a project period of up to two years with a combined budget for direct costs of up $275,000 for the two-year period. For example, applicants may request $100,000 in the first year and $175,000 in the second year. The request should be tailored to the needs of the project. Normally, no more than $200,000 may be requested in any single year.

This PA uses Just-In-Time concepts. It also uses the modular as well as the nonmodular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, applications with direct costs in each year of $250,000 or less should be submitted using the modular format. Otherwise, the instructions for nonmodular research grant applications should be followed. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

Applications submitted in response to this PA will compete with all investigator-initiated applications for funding. The participating institutes intend to commit a total of approximately $3,000,000 (total costs) per year in additional funding to this PA. The total project period for an application submitted in response to this PA may not exceed five years.

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applications submitted in response to this PA will be accepted at the standard application deadlines, which are available at http://grants.nih.gov/grants/dates.htm. Complete information on this PA is located at http://grants.nih.gov/grants/guide/pa-files/PAS-03-092.html.

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Transition to Independent Positions

An important element of the NIEHS mission is to develop exceptionally talented young scientists who are committed to understanding the impact of environmental exposures on human health. The NIEHS Transition to Independent Positions (TIP) Program is a Research Scholar Development Award (K22) program targeted to talented postdoctoral scientists. It provides a unique mechanism for attracting and supporting the transition to independent faculty positions of exceptionally talented new investigators who can impact our understanding of the problems and mechanisms associated with exposure to environmental agents in order to better protect public health. The NIEHS has determined that there is a need for a mechanism to assist exceptionally talented investigators in making the career transition from postdoctoral training to independent academic research positions. To meet this need, the NIEHS has initiated the TIP Program to facilitate the transition of the most talented postdoctoral investigators into career positions relevant to the research priorities of the NIEHS.

The NIEHS TIP Program is designed for exceptionally talented new environmental health scientists in basic, clinical, or population-based (epidemiology) research who have demonstrated outstanding scientific abilities during their training. The objective of the program is to provide support for the most promising new investigators early in their career while they establish their independent research program in a research-intensive environment relevant to the environmental health sciences. TIP investigators are expected to design and pursue their research projects independently in their area of interest. It is anticipated that the successful applicant will use the award to establish an independent research program and obtain preliminary data that will be the basis for a future research application. Specifically, the TIP investigator is expected to use the preliminary data in the environmental health sciences as a basis for an investigator-initiated research grant (R01) or equivalent to the NIH in an area of science directly relevant to the mission of the NIEHS within the first 24 months after initiation of the award.

The NIEHS has identified priority areas of research that can significantly contribute to our understanding of the impact of environmental exposure on human health. Research proposals that address one of these areas will receive a priority for funding. The current areas of special emphasis are molecular epidemiology, basic molecular mechanisms of environmental insult, genetic susceptibility and predispostion (Environmental Genome Project), human health effects of complex mixtures, reproductive health, neurodegenerative/neurobehavioral diseases and disorders, translational research, impact of environmental exposures on special populations (women, children, and minorities), and immune system modulation. Additional information about these research topics is available on the NIEHS website at http://www.niehs.nih.gov/dert/programs/special/special.htm.

Awards will be made prior to September 2005. This request for applications (RFA) uses Just-In-Time concepts. This program does not require cost sharing as defined by the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

The NIEHS intends to commit approximately $500,000 in fiscal year 2004 to fund five new awards in response to this RFA. An applicant may request a project period of up to three years and a budget for direct costs of up to $100,000 per year. Research Scholar Development Award grants are not renewable but may be extended at no additional costs at the discretion of the sponsoring institution where the TIP award has been made. Awards will be made at the institution where the postdoctoral applicant accepts a suitable position. Institutions eligible to receive awards include public or private domestic institutions such as universities, colleges, hospitals, and laboratories.

To be eligible to apply for a TIP Award, the following criteria will apply. The applicant must be 1) a current or former NIEHS Individual National Research Service Award Fellow; 2) a current or former NIH Individual National Research Service Award Fellow who is training in an area specific to the mission of the NIEHS, but whose support is from another institute, center, or division of the NIH and whose proposed research project directly addresses the effect of an environmental exposure on human illness or dysfunction; or 3) a current NIEHS Intramural Research Training Award recipient, equivalent staff fellow, or intramural clinical fellow who has competed successfully in the NIEHS intramural eligibility process. NIEHS clinical fellows with clinical or combined clinical/research degrees are eligible to apply. Clinical candidates should possess aptitudes for independent research in clinically relevant patient-oriented or population-based research areas.

Individuals with a research or health professional doctoral-level degree or equivalent with at least 18 months but not more than 72 months of postdoctoral research training at the time of application, and with demonstrated outstanding abilities in basic, clinical, or population-based research, are eligible to apply. This includes individuals with postdoctoral research experience in any environment (e.g., academic, industry, government). Individuals who have had more than six years of postdoctoral research experience are not eligible to apply. However, years of clinical training will not count against the six years of relevant research experience. Individuals who have held research or other professorship or equivalent positions in academe or elsewhere or who have been a principal investigator on either PHS research grants or non-PHS peer-reviewed research grants are not eligible to apply for this award.

The deadline for receipt of letters of intent is 13 June 2003, with 14 July 2003 the deadline for receipt of applications. Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Complete information on this RFA is located at http://grants1.nih.gov/grants/guide/rfa-files/RFA-ES-03-006.html.

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